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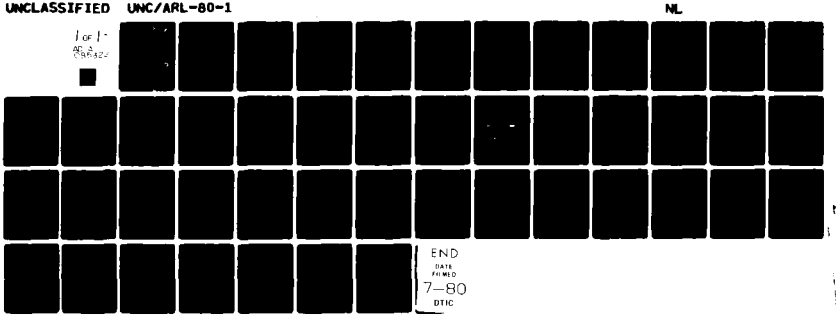

FINAL REPORT

Office of Naval Research
Underwater Physiology Program
Contracts: N00014-67-A-0321
N00014-75-C-0553

Psychoacoustic and Electrophysiologic Studies of Hearing Under Hyperbaric Pressure

Principal Investigator — William G. Thomas, Ph.D.

Co-Principal Investigator — Joseph C. Farmer, M.D.

Co-Investigator — Peter G. Kaufmann, Ph.D.

Date of Report: May 1, 1980

Auditory Research Laboratory
Division of Otolaryngology
Department of Surgery
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GENERAL STATEMENT

Since March, 1969, studies of hearing under hyperbaric conditions have been performed as a joint project by members of the Divisions of Otolaryngology at the University of North Carolina School of Medicine and Duke University Medical Center. The projects have made use of the facilities at these two institutions, as well as, the Hyperbaric Unit at Duke University Medical Center, the U. S. Navy Experimental Diving Unit in Washington, D. C., and lately, the NCSL at Panama City, Florida. These studies were funded by the Office of Naval Research, beginning in July, 1970.

Since the beginning of the research effort, a number of different projects have been completed, representing different interests in the psychophysics and electrophysiology of the auditory and vestibular systems as they relate to increased atmospheric pressures and different gas mixtures. Since the projects have been numerous and the majority have been published in various professional journals, this Final Report will make no attempt to describe in detail the various projects or the results. A summary of the various research efforts is supplied along with a bibliography of publications resulting from this contract.

SUMMARY OF WORK

1. Calibration of laboratory standard microphones -

Laboratory Standard condenser microphones have been calibrated to thirty-one atmospheres absolute (ATA) in both air and helium-air environments. Results have indicated that condenser microphones change their characteristics in relating to pressure and gas mixture. [2,7] The results of

these experiments have allowed correction factors to be derived for calibration of standard earphones and the subsequent measurement of human auditory thresholds to 31 ATA. In addition, these data have supplied correction factors for sound pressure level measurements in animal experiments.

2. Calibration of standard audiometric earphones -

Standard audiometric earphones have been calibrated to 31 ATA in both air and helium-air. Data has been collected on a total of six earphones used in various experiments. [5] These data have allowed correction factors to be derived in the measurement of human auditory thresholds under conditions of greatly increased atmospheric pressures. In addition, these data have been used by several other laboratories, including the Experimental Diving Unit in Washington, D. C. and Panama City, Florida.

3. Human auditory thresholds to 600 FSW -

Human auditory threshold measurements have been made at various depths on a total of six divers during a 600 ft. saturation dive at the Hyperbaric Unit at Duke University Medical Center. [1,6,11,12] During this dive, data was collected on air conduction thresholds, bone conduction thresholds (SAL), and frequency difference limen. These data have indicated the following:

(a) Human subjects subjected to hyperbaric helium-air environments developed a reversible conductive hearing loss which is related to depth and pressure. This appears to be caused by increased impedance of the middle ear transformer mechanism secondary to increased gas density.

(b) This conductive hearing loss seems to be greatest in the lower frequencies and least in the higher frequencies. This is possibly explained by large middle ear impedance mismatch and an upward shift in the ear resonant frequency in a helium atmosphere.

(c) The amount of hearing loss among different subjects is quite variable for some time immediately after the beginning of a helium-air hyperbaric exposure. With the passage of time, there seems to be an increasing effect on the low frequencies and less variation in the amount of hearing loss. The explanation of this is possibly related to varying rates of middle ear clearing and pressure equalization during descent. This suggests that experienced divers are indeed able to tolerate differential pressures across the tympanic membrane without significant discomfort.

(d) There is no change in bone conduction as measured by the Sensory Acuity Level (SAL) method or in the ability to match frequency in a hyperbaric helium-air atmosphere at a simulated sea depth of up to 600 feet in uncomplicated dives.

For the performance of the above described human auditory threshold measurements, the hyperbaric chambers at the Duke University Medical Center, the U. S. Navy Experimental Diving Unit in Washington, D. C., and the NCSL in Panama City, Florida were equipped and wired so that future studies can be accomplished at these facilities.

4. Human auditory thresholds to 31 ATA

Data have been collected on an additional thirty-eight divers on nine different dives at the Experimental Diving Unit in Washington, D. C. These included dives of 300 ft., four dives to 600 ft., two dives to 850 ft., and one dive to 1000 ft. [3,8,9,11,12] A total of 1160 threshold measurements were made at various depths during compression and decompression. In addition, data was collected on the SAL thresholds, Bekesy Tracings (continuous and interrupted), and surface measurements.

5. Incidence of sensori-neural hearing loss among Navy divers -

During the course of the above studies, audiograms were obtained on a large number of experienced U. S. Navy divers. A significant incidence of apparent noise induced sensori-neural hearing loss in the higher frequencies was found. We feel that a study of environmental noise levels under different diving conditions is needed. A preliminary evaluation has been made of the background noise levels under various diving conditions at the Hyperbaric Chambers at the Duke University Medical Center and the U. S. Navy Experimental Diving Unit in Washington, D. C. [11,12] In addition, noise level measurements of various diving helmets have been made utilizing the acoustic equipment and techniques described above. These studies were carried out by Dr. James Summitt at the Experimental Diving Unit. The results of these studies have been tabulated and are currently in manuscript form. These results, however, have indicated that air noise inside diving helmets and the background noise inside hyperbaric chambers during gas exchange is intense enough to cause a temporary threshold shift and possibly a permanent threshold shift to prolonged exposure. (Summitt, J. and J. Reimers. Aerospace Med. 42: 1173-1177, 1971)

6. Effects of increased atmospheric pressure on cochlear microphonics and nerve action potentials -

Experiments have been conducted on laboratory animals to 165 ft. in compressed air during compression and decompression. [11] In these experiments, electrodes were placed on the round window and cochlear microphonics and VIII nerve action potentials have been recorded to tone presentations (500 Hz and 4000 Hz). Approximately twenty guinea pigs have been tested on compressed air. Analysis indicates a drop in both the Cochlear Microphonic (CM) and Action Potential (AP) which is related to depth. This loss appears to recover after return to surface.

7. Incidence of hearing loss during saturation dives on helium-air -

An incidence study has been carried out by Dr. Summitt, Dr. Farmer, and Dr. Thomas on divers suffering sensori-neural hearing loss during saturation dives on helium-air. [16] The purpose of this study is to determine if any contributory factors seem to be common to all of these "hits". Such factors as the diving profile, depth at which the "hit" occurred, age of divers, previous history of ear pathology, ear which suffered the "hit", involvement of the vestibular system, method of treatment, etc. have been studied on the seventeen divers reported.

8. Impedance studies during increased atmospheric pressure -

Attempts were made to measure the acoustic impedance on three divers to a depth of 99 ft. on compressed air. The middle ear mechanism appears to become very stiff with only slightly increased atmospheric pressure. Therefore, stiffness of the ear exceeded the capabilities of the instrumentation ($\pm$ 400mm H_2O) by 1 ATA.

9. Animal behavioral thresholds during increased atmospheric pressure -

The auditory thresholds of the chinchilla have been measured at surface and at 33', 66', and 99' in the hyperbaric chamber, and these measures compared to thresholds in a sound-treated environment. Results indicated that thresholds in the chamber were much higher than in a sound-treated environment because of the ambient noise. Also, thresholds at 500, 1000, and 2000 Hz were significantly worse than surface thresholds at 33', 66', and 99'. The auditory threshold was a function of depth, with thresholds getting progressively worse at deeper depths. At 4000 and 8000 Hz, however, thresholds improved at deeper depths. This data agrees with human threshold data published by the current investigators.

10. Temporary Threshold Shift during increased atmospheric pressures and different breathing mixtures -

Temporary threshold shifts in the chinchilla were investigated using a stimulus of 300-600 Hz narrow-band noise at 105 dB SPL for sixty minutes, under a variety of conditions. TTS at four minutes, fifteen minutes, and thirty minutes after cessation of noise for a 715 Hz tone was measured at surface while breathing air, at surface while breathing 100% oxygen, at 66' while breathing air, and at 66' while breathing a mixture of 80% helium and 20% air. Results indicated considerably more TTS at surface, with no significant difference between air and 100% oxygen, than that found at 66'. At depth, there was no TTS while the animals were breathing HeO_2. There was a small amount of TTS measured at four minutes after the cessation of the noise while the animals were breathing air at 66', however, this was fully recovered in fifteen minutes. These results tend to indicate that breathing high

concentrations of oxygen does not protect the inner ear from fatigue. However, the animals showed little or no TTS at depth, especially while breathing HeO_2. This would tend to indicate that the lack of TTS inside hyperbaric chambers at high noise levels is a function of impedance changes in the ear and not the breathing mixture. This is especially true since no TTS was noted while the animals were breathing 80% helium.

11. Development of animal model for vestibular research -

Vestibular research activities in the laboratory at UNC have concentrated primarily on development of an animal model in which the peripheral vestibular apparatus may be directly studied in an alert animal. Two animals are being developed for this purpose - the Mongolian gerbil and the Kangaroo rat (Dipodomys). The selection of these species was prompted because of the specialized middle ear enlargement demonstrated in both of these species. This anatomical specialization is thought to be an adaptation of the auditory receptor system to environmental conditions and is not currently considered a modification of the vestibular apparatus. The tremendous middle ear enlargements of these species allow a relatively simple surgical approach to the vestibular apparatus. In addition, the bony labyrinth is an extremely thin structure, allowing further surgical manipulations for physiological and anatomical studies. Currently, work is proceeding primarily in two directions. First, surgical techniques are being developed to allow chronic electrophysiological studies of ampullar electrical activity in the alert animal. Small wire electrodes (100) are being implanted in the endolymphatic space of the horizonal semicircular canal for monitoring changes in DC resting potentials of the ampulla (Katsuke and Davis, 1954; Trinckev, 1959; Eldredge, Smith, Davis and Gannon, 1961; Sala, 1965). This work

has met with varying success, primarily being hampered by a high death rate of animals during surgery. Adoption of special protocols for anesthesia in conjunction with use of special equipment for artificial respiration have been adopted with good results. A small machine screw is cemented to the skull of these animals to provide a means of grasping the head for stabilization. Eye movements of these animals are monitored by electronystagmographic recording using either needle or chronically implanted electrodes. Once the preparation is perfected, alert animals will be observed under various stimulus conditions. The animals will be restrained in a small box and their heads rotated into a position so that the lateral semicircular canals lie in the horizontal plane. The head is held in position by clamping the end of the implanted machine screw. Controlled angular accelerations in the horizontal plane will be used as initial stimuli. Additionally, rotation of the visual and auditory environments will be employed. This research is continuing at the present time.

12. Anatomical studies in the vestibular system -

Anatomical studies are also being conducted to determine the origin of the efferent vestibular bundle in the gerbil. The technique of retrograde transportation of dye to trace anatomical pathways is used. Horseradish perosidase (HRP) has been injected into the utricle of gerbils. Following a one day survival period, the animals are sacrificed and their brains sectioned and stained. Tentative results indicate bilateral clusters of small positively stained neurons in the vestibular areas adjacent to the abducens nuclei. These findings are consistent with the earlier work of Gacek and Lyon (Acta. Otol. 77: 92-101, 1974).

Additional anatomical studies of the peripheral vestibular apparatus of both gerbils and Kangaroo rats are planned to verify similarities of these species with other mammals.

13. Effects of increased atmospheric pressure on nystagmus -

During previous studies, it has been noted that the manifestations of the High Pressure Nervous Syndrome: tremor, decrements in psychomotor performance, dizziness, and nausea; were not accompanied by true vestibular nystagmus on ENG recordings. [13] These studies have been carried to depths as deep as 1300 feet. We, thus, postulated that the dizziness and tremor of HPNS is related to a decrease in the usual cerebellar inhibitory modulation of the brainstem vestibular nuclei. This decreased inhibitory activity equally affects in the right and left vestibular nuclei resulting in increased impulse frequency over the right and left central vestibular connections, eye muscle motor nuclei, vestibulospinal tracts, and vestibulo-vagal connections with resulting nausea, ocular and limb tremor, and a partial loss of spacial orientation without true vertigo. Work during the previous year has further confirmed these results. In addition, studies of the stimulated vestibular system during the High Pressure Nervous Syndrome have just begun. If there is indeed decreased inhibitory modulation of the central vestibular connections, one would postulate that the responses to the stimulated vestibular system during the High Pressure Nervous Syndrome would be increased or altered in another manner. Recently, ENG recordings of humans during rotational stimulation were done on a dive to 1000 feet. These results are now being analyzed.

14. Management of decompression sickness -

A standardized method of management of vestibular decompression sickness has formulated and composed.[15,17] This method has been presented in January, 1976 at the Eastern Section Meeting of the Triological Society in Toronto, Canada; in February, 1976 at the Study Group of the European Undersea Biomedical Society in London; and at the Annual Scientific Meeting of the Undersea Medical Society in Miami, Florida in May, 1976. The method has been well received both in the United States and Europe. Management of divers with vestibular decompression sickness during dives in the North Sea has been accomplished by this method and verbal reports indicate that such management thus far is effective. Monitoring of divers developing vestibular symptoms during the decompression phase of diving and their subsequent treatment is continuing and the method will be refined as indicated.

15. Human Brain-stem Evoked Responses (BER) -

The brain-stem evoked response (BER) is a method of extracting information from the lower centers of the CNS. Research with stimuli delivered to the auditory system has yielded at least seven (7) evoked responses within the first 10 msec. after stimulation. The evoked responses are very small (approx. 0.25 microvolt) and, therefore, require extensive signal averaging. However, since they represent synchronous firing of neural units, it is reasonable to assume that the evoked responses arise at or near various synapses. Animal research using chronic electrodes in different auditory nuclei tend to support this assumption. The BER, therefore, has value in assessing the auditory system since it affords a noninvasive method of studying brain-stem function, including neuronal travel time and synchrony of

firing at the synapse. Although seven evoked responses have been identified in previous research, the most stable seems to be the IV-V complex, which is thought to arise from the inferior colliculus. This response is present in almost all BERs, while other responses may be present or absent in different recordings.

During past contract years, BERs were recorded from six (6) divers during a saturation dive to 1000 feet at Duke University. Auditory clicks were delivered at a constant sensation level to the right ear, left ear, and to both ears combined. In addition, a control was recorded where no clicks were presented, with the evoked response averaged in the same fashion. Figure 1 shows a summary of these results. It can be seen from this figure that shorter latencies are recorded at 1000 feet, in comparison to controls taken at surface. It can also be seen that the evoked responses are averaged to essentially a straight line when no stimuli are presented. Two possible explanations for the decrease in latency at depth might be considered. First, the increased gas density in the middle ear may produce better coupling across the middle ear space and, thus, reduce the time required to the signal to reach the inner ear. This, in essence, would produce evoked responses with decreased latencies, since the signal is reaching the inner ear earlier. Second, increased pressure, inert gas, or a combination of pressure and gas mixtures may change the travel time along neurons and, thus, reduce the latency. The latter explanation, however, has little support in other research, including somatosensory recordings. The most logical explanation appears to be that the reduced travel time occurs in the middle ear as a result of more favorable coupling and that neuronal transmission does not appear to be affected by increased pressure or inert gas.

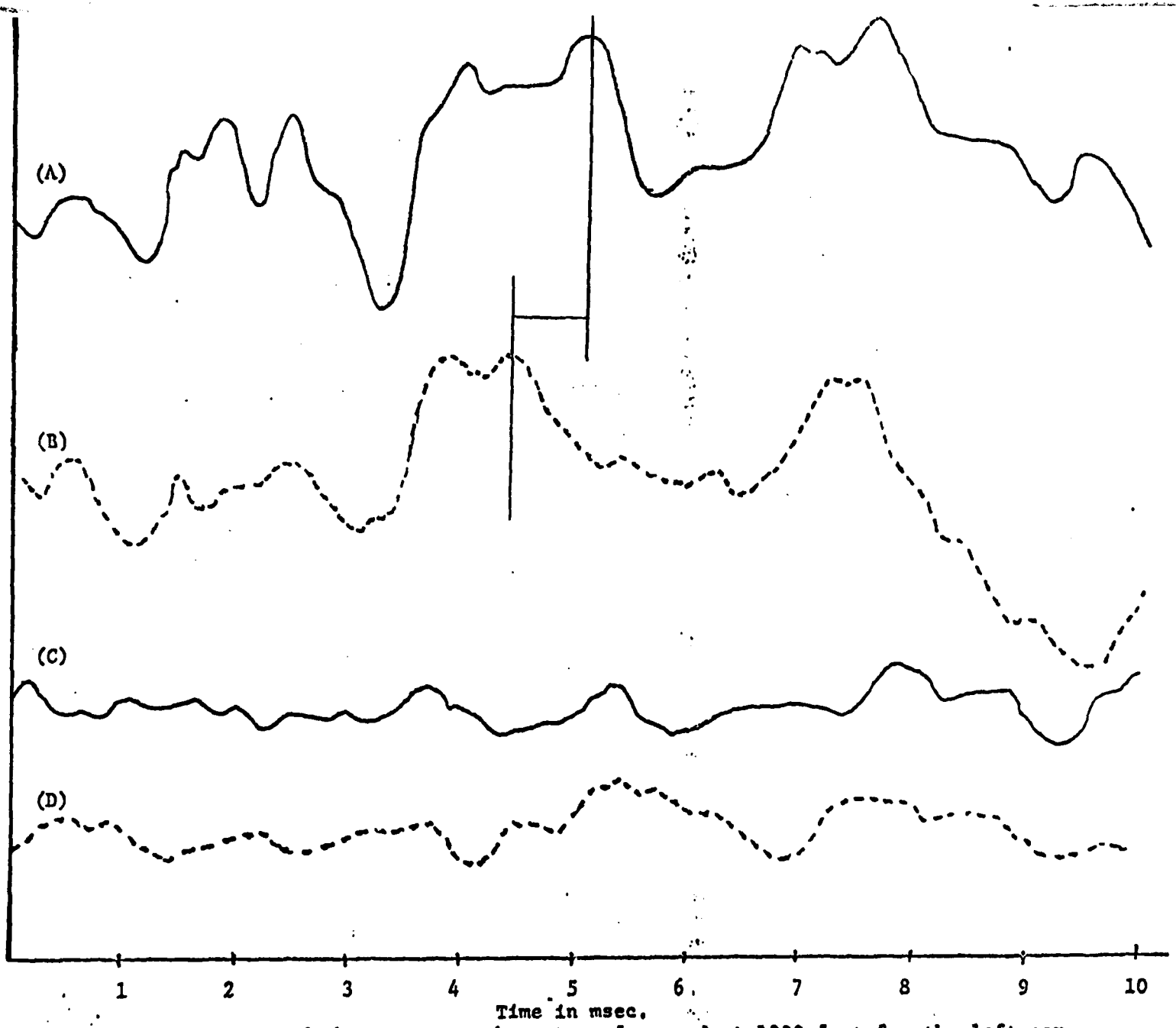

Figure 1. Brain-stem evoked responses taken at surface and at 1000 feet for the left ear (A and B) and for the control (C and D). Curve A shows the BER for the left ear at surface and curve B shows the left ear at 1000 feet. A decrease in latency can be noted in the IV-V Complex occuring about 4 or 5 msec, at depth. The two controls show no responses or differences at depth

16. Human vestibular studies -

Human vestibular work by this group consists primarily of evaluation of vestibular function during ongoing dives at Duke University. On a recent dive to 31 ATA, a complete vestibular test battery was conducted on two professional divers. The tests included electronystagmography (ENG) with postural, eye tracking and angular acceleration exercises. Angular accelerations were administered with a Barany chair arrangement utilizing the Contrave-Goerz vestibular test table. Evaluation of the data from this dive is continuing. Currently, a modified version of MITNYS (an ENG analysis program developed at Massachusetts Institute of Technology) is being implemented on the minicomputer at UNC. Following completion of this software modification, analysis of the tape recorded data will continue.

One problem that has become evident from the aforementioned dive is a lack of time to conduct a complete vestibular study during an otherwise busy dive profile. Rotational testing requires a 4 to 8 minute interstimulus interval between accelerations to control for vestibular habituation. Consequently, test times expand rapidly. Abbreviated tests, however, are not suitable due to wide variations in responses. This problem has been assessed and an alternative testing procedure is being evaluated. Essentially, this alternative consists of measuring eye-head movement coordination during active and passive rotations of the head. Basic experimental work on this reflex mechanism has been conducted in monkeys. This work indicates a highly stereotyped reflex mechanism that is easily and rapidly studied. Similar studies on humans under hyperbaric conditions may yield an effective means of evaluating vestibular and oculomotor dysfunction without consuming massive blocks of bottom time.

17. Animal vestibular function during deep dives -

During previous contract years, animal studies designed to investigate vestibular function during various hyperbaric conditions have been initiated. One series of experiments involved analysis of the electroencephalographic events in the central vestibular system of rats during deep simulated dives using helium-oxygen mixtures. [13] EEG recordings were obtained using adult male Wistar rats from electrodes in the frontal cortex, cerebellar vermis, and the superior vestibular nucleus. After control recordings on the surface using air, the animals were individually compressed to 138 ATA at HeO_2 at 40 atm/hr. Samples of EEG taken every 100 feet were subjected to power spectrum analysis. Similar changes were observed in all leads, with those in the frontal cortex showing the least variability among animals. High frequencies declined in amplitude as much as one hour prior to the onset of generalized symptoms, while low frequencies increased. Activity in the superior vestibular placement showed the greatest variability. Duration of paroxysmal activity was not significantly different among the three channels. The findings suggest that disruption of central vestibular function progresses similarly to changes seen in other portions of the central nervous system during deep helium-oxygen exposures. It was also observed that the generalized seizures noted during the convulsive end-points of these dives did not correlate with a characteristic electroencephalographic pattern. The electrical concomitants of the observed behavioral seizures varied from animal to animal, indicating a degree of variability in the mechanisms or systems through which the paroxysmal events in the central nervous system progressed during simulated deep depths.

18. Effects of cerebellar ablation on the HPNS -

In response to data suggesting a cerebellar involvement in vestibular components of HPNS and our previous study of the cerebellar electroencephalogram which was consistent with this hypothesis, [19] we conducted a study to determine whether cerebellar ablation exacerbates the HPNS. [21]

The cerebellum was surgically ablated in 22 animals, six of which survived the severe lesion with the aid of daily feeding through a permanently implanted naso-gastric tube. Electroencephalographic data was obtained by means of stainless steel electrodes implanted in the hippocampus, reticular formation, frontal cortex and, in seven normal control animals, the cerebellar vermis. The animals were compressed at 80 atm/hr to a maximum pressure of 136 ATA in a helium-oxygen atmosphere under temperature controlled conditions.

The data showed a modest but statistically significant decrease in the pressure (Pc) at which cerebellectomized animals experience HPNS seizures. Cerebellectomized animals also experienced nearly twice the number of seizures as the normal control group. We concluded that removal of inhibitory outputs of the cerebellum augmented HPNS, and that one of the effects of high pressures is to similarly affect inhibitory mechanisms of the central nervous system.

19. HPNS at the level of the spinal cord -

The relative susceptibility to HPNS of three classes of excitable tissues, skeletal muscle, peripheral nervous system, and central nervous system of intact mammals has not previously been investigated. This data is important because it provides a context in which all other studies of the HPNS and sensory systems (vestibular, auditory, visual, etc.) can be evaluated.

Data was gathered on 13 adult Wistar rats which sustained complete spinal transections at levels T-7 to T-13 two to three days prior to compression at 60 atm/hr to a maximum depth of 120 ATA. Three animals additionally received unilateral section of spinal nerves L2-L6 at their exit from the intravertebral foramena, thus completely denervating one hind limb. Electroencephalograms and electromyograms were recorded in 12 animals. [22,23]

All animals exhibited typical HPNS symptoms rostral to the transection, in some cases culminating in seizures. Caudal to the transection, HPNS progressed in a fashion similar to that observed in intact animals, becoming more intense with increasing pressure, and culminating in a seizure. Figure 1 illustrates a typical EEG and EMG segment for a spinalized rat immediately preceding and during a spinal seizure. Limbs denervated by transection of the lumbar nerves never exhibited overt fasciculations, tremors, or EMG activity.

This demonstration of substantial HPNS symptoms caudal to a spinal transection firmly establishes the syndrome's neurogenic character. It shows that HPNS depends on the central nervous system, but not necessarily the brain. Since the denervated limbs remained flaccid throughout the dive, HPNS does not appear to have a substantial myogenic component.

20. Evoked potentials in the central nervous system of alert animals at pressures to 120 ATA -

Our studies of electrically evoked potentials in the central nervous system will contribute toward elucidating mechanisms of HPNS in intact animals. Our aim is to record evoked potentials in the vestibular pathways, which are a complex network of projections involving very inaccessible peripheral nerves, several brainstem nuclei, several

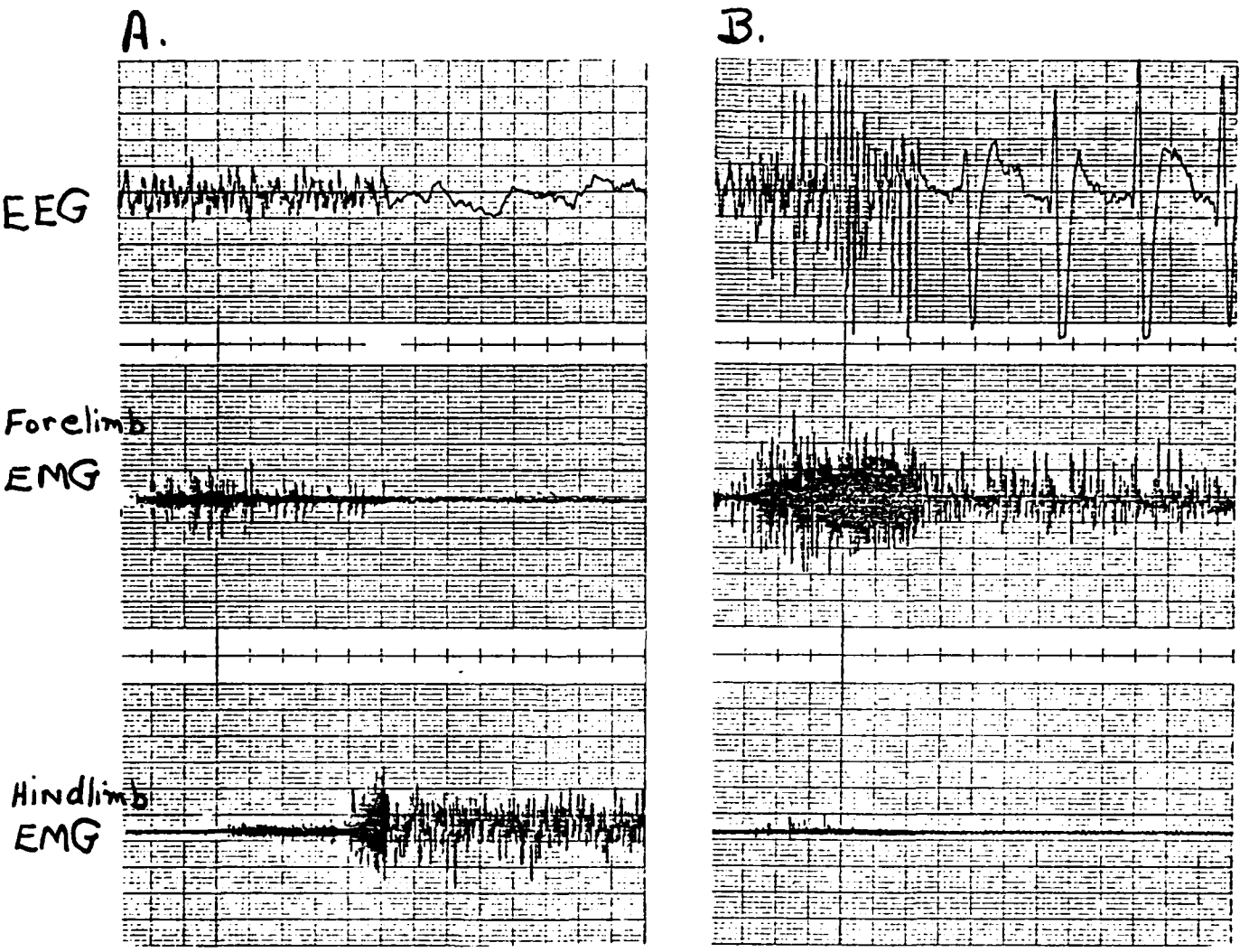

Figure 1. Two seizures in a rat with spinal transection. A: Spinal seizure resulting in extreme EMG activity in hindlimb innervated by spinal nerves caudal to spinal transection. B: cerebral seizure occurred somewhat later, and is accompanied by paroxysmal EEG and extreme EMG activity in the forelimb.

cerebellar nuclei and cortex, and the cerebral cortex. This complexity led us to first study a much simpler model, consisting of the projection from retinal ganglion cells, to the thalamus, and cerebral cortex, a system involving only three well-defined steps of processing. Information gleaned from this study will enable us to apply similar techniques to auditory and vestibular pathways, and provide a context within which auditory and vestibular data can be interpreted.

Five rabbits were implanted with electrodes in the optic chiasm, lateral geniculate nucleus (LGN) of the thalamus, and the striate cortex using stereotaxic techniques. All electrode sites were functionally verified by their response to brief flashes of light. EEG electrodes were implanted over the frontal cortex in order to monitor the condition of the animal during the dive.

After several days of recovery, the alert animals were placed in a restraining harness and compressed in a helium-oxygen atmosphere at 60 atm/hr to a final depth of 120 ATA. Potentials evoked in the LGN and striate cortex by electrical stimulation of the optic chiasm were processed with the aid of an Ortex histogram computer obtained with funds from the Office of Naval Research. Data was gathered at surface and in 10 atm steps thereafter. Examples of potentials evoked at surface, at 50 ATA, and at 100 ATA are provided in Figure 2. It can be seen that the greatest changes occur in the latency of the late component.

The experiments are continuing, and final interpretation of results will take place at a later date.

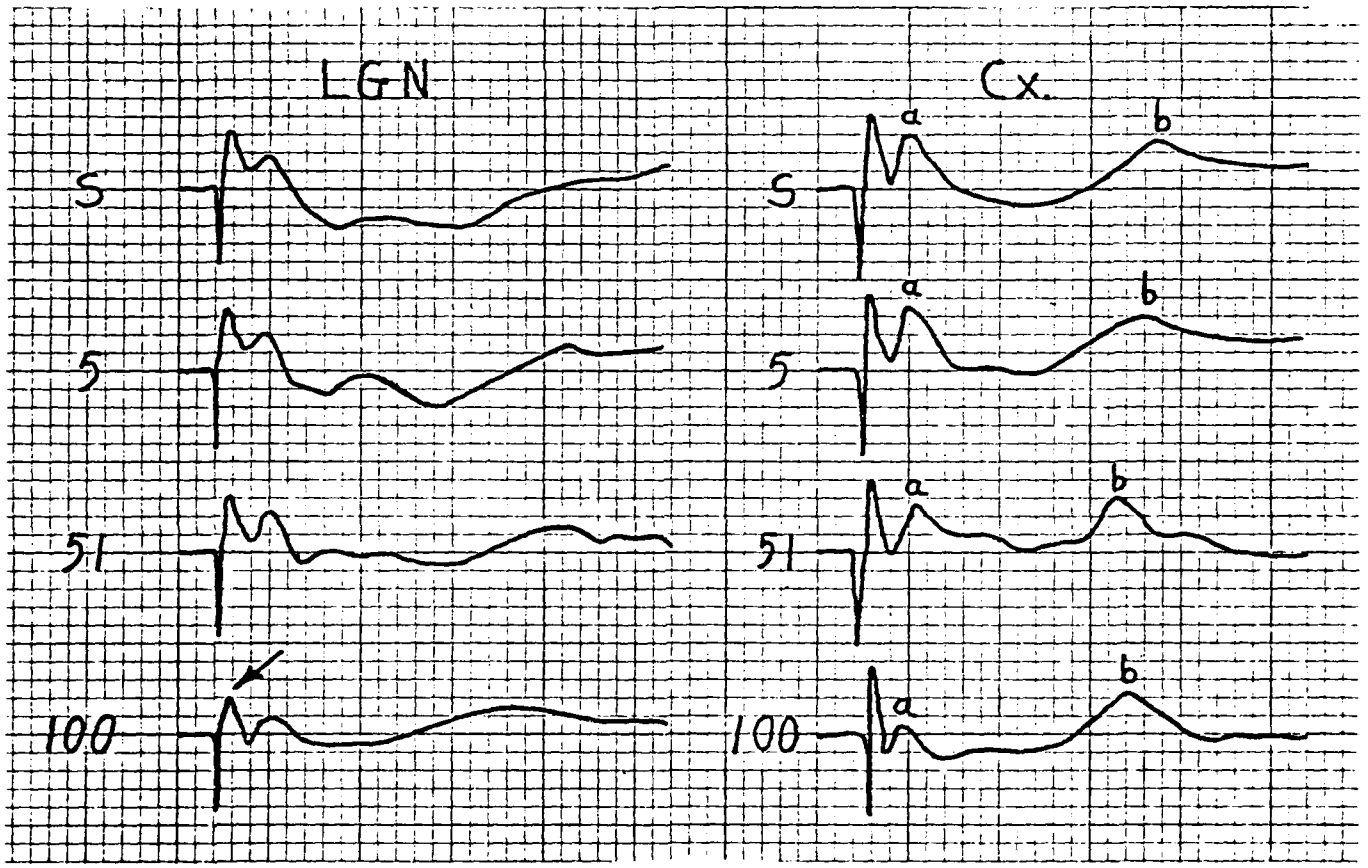

Figure 2. Evoked potentials in the geniculo-striate system at surface (S), 5 bars, 51 bars, and 100 bars. Little change occurs in the averaged evoked potential in the lateral geniculate nucleus (LGN) until 100 bars of pressure, at which point there is a moderate reduction in the amplitude of the primary component (arrow). In the cortex (Cx), the late component (b) shows a decreasing latency with pressure. The second component (a) shows a substantial reduction in amplitude and latency at 100 bars.

21. Recording from single cells in the vestibular pathways at pressure -

Monitoring activity of neurons in the vestibular pathway can potentially provide information leading to an understanding of the origin of vestibular symptoms in diving, particularly those of the HPNS. Our primary target area at this time are cells in the vestibulocerebellum. These cells exert inhibitory modulation over the vestibular nuclei, and are those most likely to be involved in disinhibition phenomena.[11,20]

These experiments are very difficult under hyperbaric conditions, but are progressing. Experiments to date have been exploratory in nature, or have tested equipment necessary for this work.

Considerable time has been expended in testing hydraulically operated micromanipulators designed for delicate adjustments of the microelectrodes used for isolating and recording electrical activity of the cells. A unit manufactured by F. Haer and Co. was found to be adequate, and has been acquired with funds from other sources.

Pilot experiments have been performed in anesthetized cats, in which successful isolation and recording from single cells in the cerebellar cortex was achieved (Figure 3). It became clear that an anesthetized preparation is both exceedingly difficult to maintain at pressure and unreliable, since pressure reverses anesthesia. Consequently, we have experimented with a surgically implanted chamber over the cerebellum, allowing access to the brain of awake animals at a later time. This technique is now ready for use.

Since monitoring of single cell responses per se yields uninterpretable data, and stimulation of an awake animal is difficult, we have explored other methods that might be adapted to these needs. We are now preparing to use iontophoretic administration of neurotransmitters as a means of testing the responsiveness of cells at pressure.

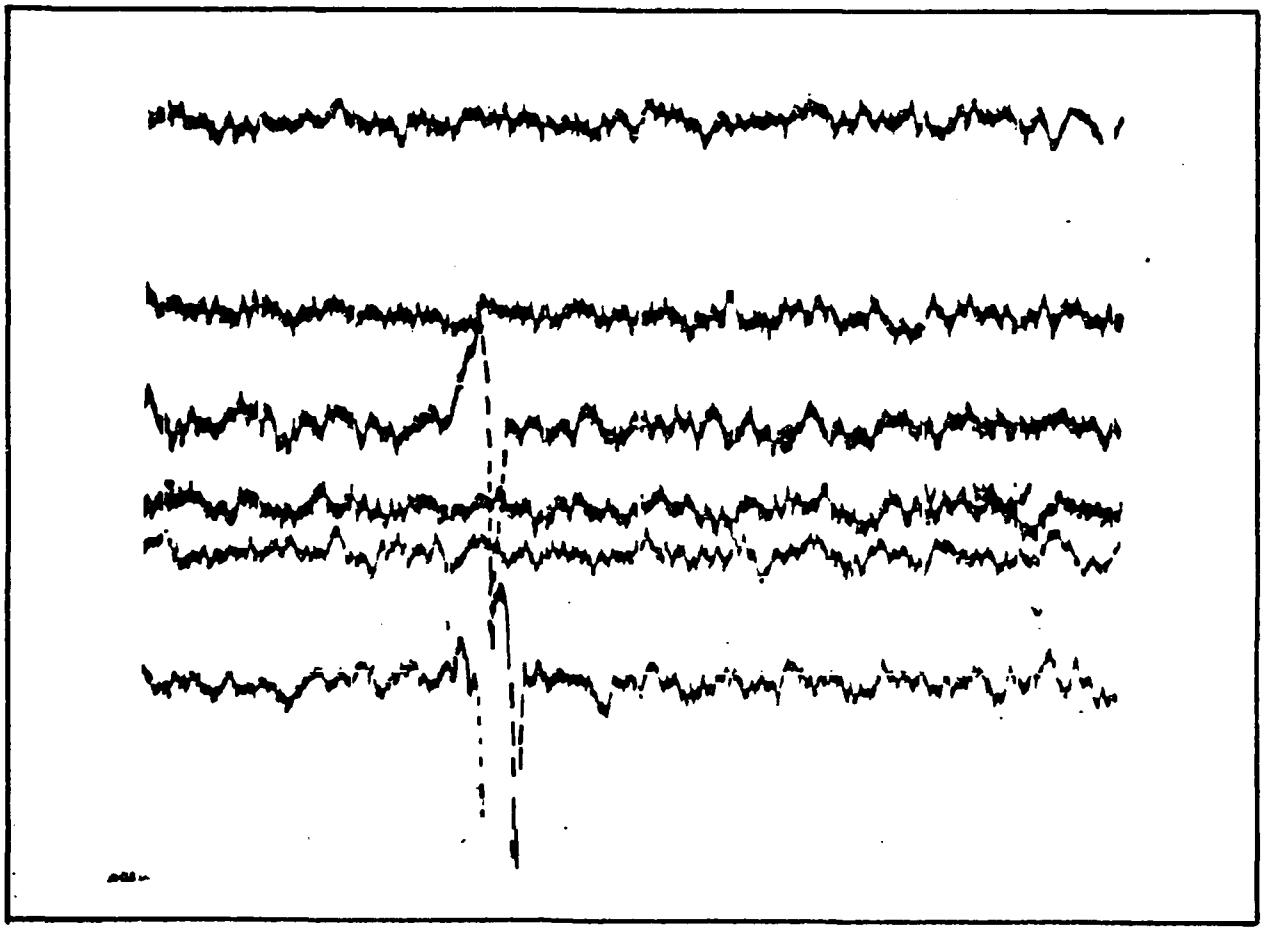

Figure 3. Single cell activity recorded from the cerebellar cortex of an anesthetized cat at 30 bars. The doublet in the lower trace is a Purkinje cell.

22. Measurements of pressure in various inner ear compartments -

These experiments are being undertaken in order to test whether high pressures of helium and/or inert gas switches result in changes in inner ear pressure (endolymph and/or perilymph), a condition which would lead to abnormal vestibular output of the central nervous system.

A sophisticated pressure measuring device has been acquired with funds from other sources, and has been tested several times. Since measurements will require prolonged monitoring, a perfectly balanced instrument, with virtually no drift, is required. The most recent instrumentation test revealed a successful two hour drift free performance under simulated conditions. We are encouraged that the instrument will function as anticipated, but these tests need to be repeated.

The mongolean gerbil has been chosen as the animal model due to the accessibility of the semicircular canals within the bulla. Several animals have been dissected, and minute fenestrae placed in the wall of the horizontal canal, the target of the measuring probe. We can now successfully insert the measuring probe into a semicircular canal with the aid of a micromanipulator.

Further tests are being conducted to ascertain the reliability of the instrumentation, since the tissues involved are very delicate, and pressures to be measured are expected to be small.

23. Auditory brain-stem evoked potentials in alert animals -

A case has been made for the similarity in site of action, if not in direction of change, between inert gas narcosis and HPNS. It appears likely that the site of action of narcosis and HPNS in the brain is the synaptic junctions at various nuclei and involves interference with

electrochemical transmission across synapses. The initial manifestation of HPNS seems to be neuromuscular signs, such as tremor, which varies in affected muscle activity, severity and depth at onset with compression rate. More generalized impairments can also be seen, however, in higher cerebral functioning. These include: loss of attentiveness; change in EEG pattern; changes in cognitive or mental performance; long term memory; and, dizziness with occasional vertigo and nausea.

Animal experiments in HPNS seem to show general patterns, although some variability exists, along with some species differences. In general, HPNS is initially manifested as tremors, progressing to myoclonic episodes and to generalized clonic seizures with continued compression. Further compression usually results in generalized tonic seizures, coma and death. It would appear, therefore, that at some depth this syndrome becomes irreversible. Susceptibility to HPNS in different species appears to increase with increasing complexity and development of the CNS. EEG patterns in animals have shown the same general pattern as similar studies in humans, e.g. decrease in alpha activity and an increase in theta activity. A difference is noted in animals, however, when recordings are made from implanted electrodes in the brain, thalamus and brain-stem. While the activity in the cortex appears to be depressed, hyperexcitability appears in thalamic and brain-stem areas. This is an interesting observation which has many ramifications for additional research in HPNS in animals and humans. For animal experimentation to be relevant in predicting possible human limitations in regard to depth, adequate animal models must be developed and the apparent disparities between animal and human research must be resolved. Currently, investigation

is underway to measure sub-cortical evoked EEG activity in humans, which may help to resolve some of the apparent disparities.[18] These relatively stable brain-stem evoked potentials in humans offer great possibilities for resolving some of the apparent disparities and advancing research on the effects of HPNS on sub-cortical nuclei.

Until the early 1960's, the EEG was the only technique available to the neuroscientist and brain physiologist for the study of the electrical activity of the human cortex. While EEG has proven useful both for the study of brain function and the clinical diagnosis of neurological disorders, it has been inadequate for any rigorous analysis of the electrical signals of the human brain which are concurrent with repetitive presentations of specific stimuli such as light, sound, or touch. Presentation of an auditory, visual or somatosensory stimulus produces a transient change called an evoked response (ER) in the electrical activity of the brain. ERs can be recorded from electrodes implanted at sites of interest in the brains of animals or from electrodes attached to the scalp of humans. The latter technique provides a convenient, non-invasive window on CNS function in humans. Evoked responses to individual stimuli are generally too small to be distinguished from spontaneous activity of the brain. Computer-averaging techniques are currently available to extract the desired "signals" from the background "noise" of the brain. The averaging process is predicated on the assumption that ERs to successive repetitions of the same stimulus are constant in form and latency while background EEG is random in time with respect to stimulus onset. Thus, if a series of EEG segments time-locked to stimulus onset are superimposed mathematically, random background activity will sum to zero, leaving the

stimulus-evoked response. The "signal" extracted in this manner is called "average evoked response" (AER).

One of the more stable evoked potential measures is the brain-stem response. This is a series of vertex-positive waves following a click or tone burst with latencies from 1-10 msec. To date, seven different waves have been identified and associated with various nuclei in the auditory brain-stem system. The most prominent and visible wave of this series occurs with a latency of approximately 6 msec and is called the V Wave. It is assumed to originate in the inferior colliculus, and is a good candidate for assessing the higher auditory frequency responses occurring in the basal turn of the cochlea. Other waves have been ascribed to the auditory nerve (Wave I), cochlear nucleus (Wave II), superior olivary complex (Wave III), lateral limniscus (Wave IV), medial geniculate (Wave VI), and radiation from medial geniculate (Wave VII).

Because of questions raised regarding contributions of the cortex and brain-stem nuclei during HPNS, a series of experiments were initiated using the auditory brain-stem evoked response (BSER). The animal model chosen was the chinchilla. The methodologies for recording BSERs in the chinchilla, implanting electrodes, and stabilizing the head have been worked out during past contract years. Also, a considerable amount of BSER data has been collected on the chinchilla at surface in our laboratory. This data has proven to be extremely stable from animal to animal and from day to day in the same animal. Much of the work in the current contract year has involved design and fabrication of instrumentation, redesign of methods to hold the animal, and calibration of transducers.

One important consideration was design of a stable, low-noise biological amplifier that would operate without excessive noise or drift under great pressure and temperature changes. This project was completed and the amplifier tested and calibrated to 74 bars. Another problem was associated with the skull-mounted bolt for stablizing the animal. It was found that involuntary movement during HPNS would dislodge the bolt, usually resulting in loss of electrodes. It was finally decided to use a snug body sling to maintain the animal. Although the animal was free to make some movements, it was generally maintained throughout the experiment. A laboratory standard condenser microphone (Bruel & Kjaer, mdl. 4145) and a standard audiometric earphone (Telephonics, mdl. TDH-39) were calibrated to 74 bars under identical conditions to the experimental paradigm. The condenser microphone was calibrated with an electrostatic actuator in a method identical to that previously described [2] and used to calibrate the earphone transducer.

Recording of BSERs from three animals was attempted with questionable results. The animals were placed inside a 208 liter pressure vessel, suspended in a body sling. Wire hook electrodes were placed on the vertex and on each mastoid. During compression, 0.1 atm of oxygen was added to the chamber at surface and the chamber compressed on helium. This method has been found satisfactory with small animals in maintaining the appropriate HeO_2 percentages during compression. The chamber was compressed at 1 atm per minute to 74 bars with stops at various levels for recording. Two runs were made on each animal at each stop. In addition to evoked potentials at surface, these included 10, 20, 28, 38, 48, 56, 65 and 74 bars. Animal temperature, as measured by a rectal probe, remained stable throughout the experiment and ranged from 101°F to 99.0°F.

Some visual evidence of HPNS was noted at 56 bars. This became very obvious at 65 bars, with muscle movement and spikes in the ongoing EEG recording. By 74 bars, severe tremors were noted, with wide fluctuations in the EEG.

The results of this attempt are unsatisfactory. Animal movement, particularly beyond 56 bars, injected frequent and severe artifacts in the EEG record which made analysis of the evoked potential impossible. It is still believed that brain-stem evoked potentials can supply valuable information concerning the origin and time course of HPNS. However, additional study will be required to modify the experimental methodology to insure elimination of movement artifacts.

24. Effects of pressure on signal processing in the central nervous system -

Perhaps the most striking influence of high pressures on biological processes is expressed in alterations of function of excitable tissues, such as changes in muscle tension (Cattell and Edwards, J. Cell. Comp. Physiol., 1:11-36, 1932), or the excitability and conduction velocity in nerve fibers (Grundfest, Cold. Spring Harbor Symp. Quant. Biol., 4:179-187, 1936). In the intact animal, the underlying biophysical and biochemical alterations affect the basic elements of the nervous system - membranes, synapses, and so forth, and translate into a complex chain of events which manifest themselves in symptoms called the High Pressure Nervous Syndrome (HPNS, Brauer, Ocean Industry, 3:28-33, 1968), which includes vestibular symptomatology.

Anatomically, the brain is known to be organized into regions subserving specific functions. Even though extensive reciprocal connections exist between regions serving different, as well as, similar functions, abnormal discharges have been thought to frequently occur as a result of

sudden changes in a limited region of the central nervous system, often in the cerebral cortex. This possibility must also be considered in the case of symptoms of hyperbaric origin. The aim of this paper is to examine the results of a series of experiments in the mammalian nervous system and arrive at some estimate of the anatomical structures or systems most affected by exposure to high pressure.

The cerebellum - Electroencephalographic recordings show that the typical spike-and-wave pattern of pressure-induced seizures can be recorded simultaneously from every structure so far examined: the cortex, hippocampus, red nucleus, cerebellum, reticular formation and vestibular nuclei.[14,19,21] We found the participation of the cerebellum particularly interesting, because a number of authors had suggested that the cerebellum is involved in terminating or modulating seizures (Cooke and Snider, Epilepsia, 4:19-28, 1955). Its dysfunction is also believed to contribute specifically toward the vestibular symptoms of HPNS.[10] When we compared the effects of pressure on normal rats with those on rats with cerebellar ablations, we found modest changes in the convulsion threshold pressure: normal animals seized at 99 bars, while cerebellectomized rats seized at 89 bars and sustained about twice the number of seizures. The fact that HPNS convulsions were aggravated by cerebellar removal is consistent with the hypothesis that one of the effects of pressure is a decrease in cerebellar inhibitory tone. However, the relatively modest change in seizure threshold, although statistically significant ($p < .05$), and the similarity of other HPNS symptoms in both groups, suggests that the fundamental processes resulting in HPNS proceed in substantially unaltered fashion despite extensive removal of a major structure of motor control. This was not

entirely unexpected: since pressure is uniformly applied to the entire organism, neural functioning would still be altered in the enormous pool of cells which constitute the remainder of the CNS. When excitability reaches a critical level, it tends to do so simultaneously throughout the pool, and hence the seizures. The capacity of the cerebellum in modulating this pervasive process seems to be relatively small.

Most studies on tissues in vitro require relatively high pressures, above 200 bars, to affect parameters such as action potential amplitude and conduction velocity, or membrane resistance and capacitance. The question then arises as to the size of the neuronal pool necessary to bring about a maximal response, or seizures at the lower pressures (100 bars) usually effective in intact mammals. One way this question can be addressed is to examine the progression of HPNS in limbs served by the distal portion of a transected spinal cord, thus eliminating all influences from the higher centers.

The spinal cord - Long ago Ebbeck (Pflug. Arch. ges. Physiol., 237:785-789, 1936) reported that high pressure continued to evoke spontaneous contractions in the hind limbs of spinalized frogs, but this finding could not be verified in liquid-breathing spinal mice (Kylstra, Science, 158:793-794, 1967). We performed the experiment in rats breathing a helium oxygen mixture. Twenty Wistar rats were implanted with EEG electrodes over the frontal cortex and allowed to recover. In 16, the spinal cord was transected at levels T7-T13, and four served as unoperated controls. The animals were allowed to recover for three days, during which time spinal withdrawal reflexes recovered so that clearly defined responses were evident to painful stimuli. In three

of the spinalized animals, spinal nerves L2-L6 were sectioned after exiting the intervertebral foramina, thus totally denervating one hind limb.

On the day of the experiment, the animal was suspended in a whole-body sling with all limbs hanging free and secured inside a 208 liter pressure vessel. Needle EMG electrodes were placed in both hind limbs and one fore limb. Compression took place in a HeO_2 atmosphere at 1 bar/min, to a maximum pressure of 120 bars.

Symptoms of HPNS (tremors and myoclonic jerks) in the fore limbs of spinalized animals were indistinguishable from those of intact animals, becoming progressively more intense with increasing pressure. This pattern was also observed caudal to the lesion, but at a much lower intensity.

In all animals, increased EMG activity was usually evident at about 30 bars; onset of visible symptoms progressed from mild fasciculations at 50-75 bars, to tremors and myoclonic jerks, and seizures between 90 and 110 bars (Figure 1). Limbs whose spinal nerves had been sectioned, on the other hand, remained flaccid throughout the pressure exposure. Activity profiles constructed by computing the area encompassed by EMG records at 10 bar intervals revealed fluctuation of intensity with increasing pressure, suggesting that the effects of pressure do not progress in a linear fashion throughout a given exposure. No evidence was seen that the threshold for pressure effects at the spinal level is different from that in the brain. Furthermore, it is evident that the neuronal pool of the spinal cord is sufficient to sustain massive, synchronized discharges, but that the peripheral nerve-muscle system has a much higher threshold. These results are consistent with the

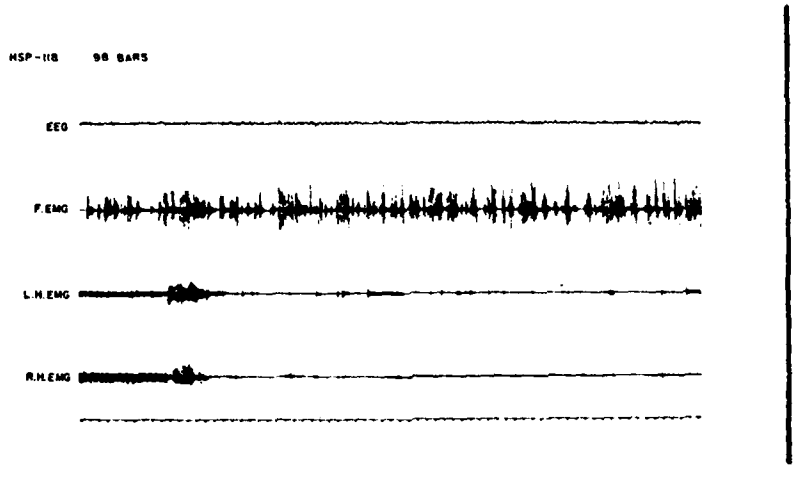

Fig. 1. A sudden burst in the electromyogram (EMG) of both hindlimbs (L.H. EMG, R.H. EMG) of a rat with a complete cord transection reveals a spinal seizure at 98 bars of pressure. No change is seen in the EEG. Intense tremor in the frontal limbs (F. EMG) continues uninterrupted. Lowest trace indicates 1 sec intervals.

concept that pressure affects identical neural elements in the same way regardless of where they happen to be located. The expression, or the consequences of these effects, however, depends on the organization of these components, and this can be demonstrated further by means of evoked potentials recorded at different points of a pathway.

The visual pathway - We chose for this study the geniculo-striate pathway of the guinea pig. Stainless steel electrodes were implanted in the optic chiasm (o.c.), lateral geniculate nucleus (l.g.n.) of the thalamus, and the striate cortex (s.cx.). The position of each electrode was functionally localized by recording its characteristic response to photic stimulation. After several days of recovery, short-latency responses of the l.g.n. (< 10 msec) and s.cx. (< 50 msec) were recorded to electrical stimuli (10-100μA, .02-.05 msec duration) applied to the o.c. Amplified, 32 response sequences were summed by means of a signal averaging computer. Responses to pressures up to 100 bars HeO_2 in 10 bar increments were compared with responses at surface, at a variety of stimulus intensities. Interpretation of the presynaptic and postsynaptic components of the evoked potentials was based on classical criteria.

At the l.g.n., exposure to pressure resulted in virtually no changes in the latency of either the presynaptic or postsynaptic components of the evoked responses (Figure 2A), which correlated nearly perfectly with small excursions of temperature recorded during the experiments. Occasionally, the postsynaptic responses also showed a decline mimicking the effects of synaptic fatigue. While the effects of pressure on the evoked responses recorded at the LGN were modest, the effects at the cortex were dramatically different. Latency changes were very similar

to those seen at the geniculate, and correlated with temperature. The amplitudes of the postsynaptic cortical response, however, increased as early as 30 atm, and attained values of up to 300% with increasing pressure, until the seizure threshold was reached (Figure 2B). Following a period of post-ictal depression, the process of amplitude augmentation was again repeated. By varying the stimulus intensity and duration, it was possible to compare response thresholds at surface and at 50 bars pressure. Again the effects of pressure at the lateral geniculate were modest. At the cortex, amplitude changes were a function of the stimulus intensity, becoming greater for strong than for weak stimuli and suggesting a change in excitability of the cortical elements.

These results support the concept that the excitatory effects of high pressures depend on organization of the local neuronal circuitry, such as the presence of recurrent excitatory collaterals, and perhaps the size of the neuronal pool available for their expression. At the same time, the occurrence of seizures in the spinal cord, as well as, the paroxysmal spike-and-wave pattern simultaneously recorded throughout many structures in the brain provide strong evidence that HPNS does not have a focal origin in the CNS. Peripheral nerves, the neuromuscular junction, and muscle fibers themselves, on the other hand, are more resistant to pressure, as evidenced by the total lack of activity in our denervated limb preparations. Their participation in the evolution of the complete syndrome is, therefore, relatively minor and depends largely on input from the central motor pathways. At the higher levels of the nervous system, such as the cortex, pressure may enhance tendencies for synchronized neuronal discharges, as reflected by the

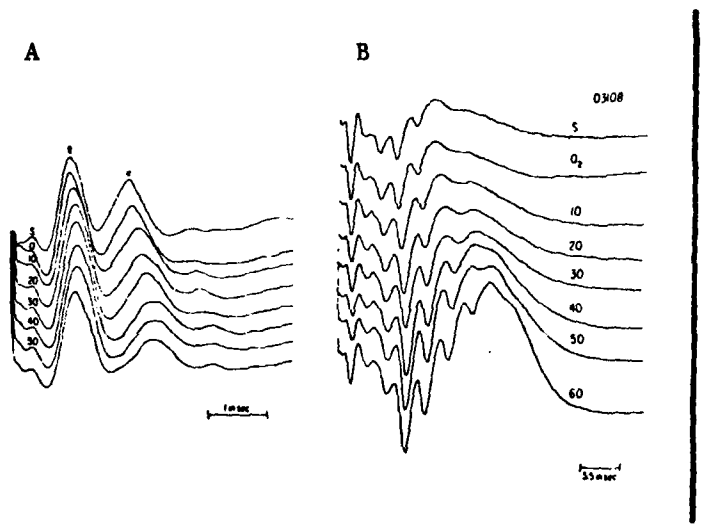

Fig. 2. Evoked potentials recorded at the lateral geniculate nucleus (A) and the striate cortex (B) of a guinea pig between 1 bar (S) and 60 bars pressure, in He-O_2. t: presynaptic, tract response; r: postsynaptic, radiation response. See text.

progressive augmentation of delta and theta activity in the electroencephalogram (Bennett and Towse, Electroenceph. Clin. Neurophysiol., 31:383-393, 1971; Kaufmann et al., Undersea Biomed. Res., 4: 391-402, 1977) and the greatly facilitated cortical evoked responses seen in our studies. It is likely that synaptic processes, such as the time course of release of transmitter substances at presynaptic terminals, their action at the subsynaptic membrane, and their inactivation or re-uptake play a prominent role in the events leading to a generalized state of hyperexcitability throughout the central nervous system, as well as, abnormal neuronal discharges in specific neuronal structures such as the vestibular pathways.

Temperature - Some of the effects of pressure could be observed or confounded by changes in brain temperature in the experimental animals when exposed to helium gas mixtures, which are known to have a high thermal capacitance. Because rectal temperature is the easiest to obtain, it has frequently been taken to represent core temperature and implicitly used as an indicator of brain temperature in studies of high pressure effects on the central nervous system. There is no assurance, however, that rectal temperature is indeed representative of brain temperature, particularly in helium environments. Since the relationship between rectal temperature and that of the brain in helium atmospheres has not previously been studied, we endeavored to determine to what extent these temperatures parallel each other. [25]

We measured brain and rectal temperatures in guinea pigs exposed to helium-oxygen environments up to 50 bars of pressure. Very high correlations ($r = .856$, $p << .001$) between the two values were observed, with an average difference of $0.47° \pm 0.31$, SD. Brain temperature was

usually higher than rectal. At a given ambient temperature, heat loss at 50 bars was more rapid than at 20 bars, supporting existing data at lower pressures. At 50 bars, normal equilibrium temperatures (~39°C) could be maintained only if ambient temperature was in the vicinity of 35°C. Therefore, if rectal temperature is adequately controlled, brain temperature can also be assumed to be stable for most experimental purposes.

RELATED STUDIES

Pressure and nitrogen narcosis -

The effects of high helium pressures in reversing narcosis are well documented behaviorally and biophysically, but not electrophysiologically. Sensory evoked potentials in the visual pathway were, therefore, tested for the occurrence of this phenomenon. [28] Electroretinographic, optic chiasm, and visual cortex potentials were monitored in the awake guinea pig as nitrogen pressures were raised to 16 ATA and held for 30 minutes. Pressurization to 90 ATA with helium in 10 ATA increments followed. We sought to a) quantify the depressant effect of nitrogen on the retina as compared to the central visual pathway, and b) to test for pressure reversibility. The electroretinogram was reduced approximately 15%, the chiasm potential by 15%, and the cortical response by 32% in 16 ATA nitrogen, and latent periods for the three signals increased an average of 5 - 8%. Helium at pressure did not restore the amplitude of the electroretinogram or optic chiasm response, but the visual cortex potential returned to control levels near 90 ATA total pressure. Reversal of the nitrogen-induced latency increases by helium was partially effective up to 40 ATA. Control latent periods were not reached. Further attenuation

of the electroretinogram and chiasm response amplitudes, and increased latencies of all signals were observed at 50 - 90 ATA.

Restitution of pre-narcotic amplitudes of the cortical evoked potential at high pressures could involve the release of inhibition from peripheral sense organs on the central pathways. The modification of the light-evoked potentials of the guinea pig's visual system by two different anesthetics, pentobarbital and halothane, is so unlike the changes observed in high-pressure nitrogen that postulation of common mechanisms is disallowed. It can only be concluded that the anesthetized unconscious state is accompanied by larger rearrangements in central excitatory vs. inhibitory neural interactions than are characteristic of the narcotized state, where a general depression of transynaptic conduction in peripheral (retinal) and central neural pathways presumably occurs.

Pressure, ketamine, diazepam, and pH. -

Emergency treatment under hyperbaric conditions, including surgery under general anesthesia, is a possibility as deep diving activities accelerate. Ketamine appears to be more resistant to pressure reversal than barbiturates, and diazepam has been proposed as a supplementary drug. The interaction of ketamine and pressure with and without diazepam as premedication was, therefore, examined in rats breathing helium-oxygen at pressures up to 90 ATA. [26] No pressure reversal of the analgesic effect was found. Premedication with diazepam failed to improve the analgesic action of ketamine, but did influence the respiratory pattern. Blood gas analyses showed a marked relationship between arterial pH. and the ketamine dose required for stable anesthesia.

Ketamine was found to have a substantial influence on the intensity of HPNS and is an ever more robust antagonist when given in combination with diazepam. This observation should be pursued with further experimentation to evaluate the potential of ketamine as a means of alleviating serious attacks of HPNS.

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UNCLASSIFIED
Security Classification

DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY (Corporate author)
Auditory Research Laboratory, Div. of Otolaryngology
Department of Surgery
University of North Carolina School of Medicine

2a. REPORT SECURITY CLASSIFICATION
UNCLASSIFIED

2b. GROUP
AD-A085322

3. REPORT TITLE

(6) PSYCHOACOUSTIC AND ELECTROPHYSIOLOGIC STUDIES OF HEARING UNDER HYPERBARIC PRESSURE

4. DESCRIPTIVE NOTES (Type of report and inclusive dates)
Final Report (1 June 1970 to 30 November 1979)

5. AUTHOR(S) (First name, middle initial, last name)
(10) William G. Thomas
Joseph C. Farmer
Peter G. Kaufmann

6. REPORT DATE
(11) 1 May 1980

7a. TOTAL NO. OF PAGES
41

7b. NO. OF REFS
32

8a. CONTRACT OR GRANT NO.
(12) N00014-67-A-0321,
N00014-75-C-0553

b. PROJECT NO.
NR 101-027

c.
NR 201-016

d.

9a. ORIGINATOR'S REPORT NUMBER(S)
(14) UNC/ARL-80-1

9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)

10. DISTRIBUTION STATEMENT
Approved for Public Release: Distribution Unlimited

11. SUPPLEMENTARY NOTES

12. SPONSORING MILITARY ACTIVITY
Office of Naval Research
Department of The Navy
Arlington, Virginia 22217

13. ABSTRACT

as follows:

This Final Report covers work performed under Contracts ~~N00014-67-A-0321~~ and N00014-75-C-0553 from 1 June 1970 ~~to 30 November~~ 1979. Work performed includes:

(1) Calibration of standard microphones and earphones;
(2) Measurement of human auditory thresholds;
(3) Studies of human vestibular disturbances;
(4) Animal electrophysiology; and
(5) HPNS.

410867

DD FORM 1 NOV 65 1473 (PAGE 1)
S/N 0101-807-6801

UNCLASSIFIED
Security Classification

14. KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
Auditory Thresholds						
Audiology						
Transducer Calibration						
Auditory Physiology						
Vestibular Physiology						
High Pressure Nervous Syndrome						